peptide; and (iii) cytotoxic T cells, under conditions conducive to the activation of cytotoxic T cells;

(b) comparing the activation *in vitro* of said T cells with the activation *in vitro* of T cells in the absence of said plurality of molecules,

wherein a lower or higher degree of activation indicates that one or more molecules in said plurality of molecules modulates the ability of the alpha (2) macroglobulin -expressing cells to stimulate the activation of cytotoxic T cells against the peptide.

75. (new) The method of claims 70, 71, or 72, wherein the activity is measured by a cytokine release assay.

76. (new) The method of claims 13, 69, 70, 71, 72, 73, or 74, wherein the alpha (2) macroglobulin receptor is recombinantly expressed in the cell.

REMARKS

Claims 1-23 were pending in the instant application. By this amendment, claims 15 and 16 have been canceled, claims 1, 2, 11, 13, 14, 17, 18, 19, 21, and 22 have been amended, and new claims 64-76 have been added, to clarify the invention. In particular, claim 17 was amended by deletion of step (a) and the terms "analog, derivative or mimetic" in step (b) for lack of antecedent support in claims 1 and 13, and/or redundancy.

The amendments are fully supported by the specification and claims as originally filed, and, as such, no new matter has been added. In particular, support for the amendments can be found at the following portions of the specification.

Claims	Claim Recitation	Support
1, 13	• recites a purified heat shock protein, or a purified heat shock protein peptide complex.	page 9, line 17; and page 15, line 17.
	• recites a purified heat shock protein fragment.	page 13, lines 26-33.
	• recites a purified heat shock protein peptide complex.	page 15, lines 7-15; page 25, lines 3-10; page 38, lines 4-8; page 34, line 7; and page 26, lines 31-33.

Claims	Claim Recitation	Support
14	• recites the method wherein the activity measured is binding of alpha (2) macroblobulin receptor to a heat shock protein.	page 25, lines 17-20.
64	• recites a purified alpha (2) macroblobulin receptor.	page 15, line 17; and page 31, line 6.
65	• recites alpha (2) macroblobulin receptor gene expression.	page 28, lines 3-13; and page 53, lines 29-32.
66	• recites alpha (2) macroblobulin receptor gene product expression.	page 28, lines 3-13; page 10, line 26-34.
67	• recites a purified derivative, analog, fragment, or domain of the alpha (2) macroblobulin recptor.	page 31, line 17.
69, 70, 71	• recites methods for identifying compounds using antigen presentation assays.	page 32, line 18.
68, 72, 73, 73, 74	• recites a method for identifying compounds using assays for activation of cytotoxic T cells.	page 26, line 25; and page 69, line 32.
	• recites an assay for cellular uptake of HSP.	page 32, line 5.
	• recites Downstream signaling assays.	page 33, lines 1-30.
	• recites calcium ion concentration assays.	page 33, line 20.
75	• recites a cytokine release assay.	page 27, lines 1-2; page 32, lines 30-32; and page 34, lines 10-28.
76	• recites recombinantly expressed alpha (2) macroglobulin receptor.	Section 5.1.1 at page 16; page 10, lines 18-25; and page 15, line 17.

Therefore, claims 1-14, 18-23 and 64-76 are pending in the instant application. A marked-up version of the claim amendments is attached hereto as Exhibit A, showing deleted matter by brackets and added matter by underlying. A copy of the claims as pending is attached hereto as Exhibit B. Applicant respectfully requests that the amendments and remarks made herein be entered into the record of the instant application.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Applicant respectfully asserts that these rejections have been obviated or overcome, or are in error, for the following reasons.

The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). Thus, according to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamide Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985).

First, with respect to the rejection on page 2, ¶ 4A of the Office Action, claims 1 and 13 were rejected for indefiniteness of the term "receptor activity", because, according to the Examiner, the metes and bounds of the claim are unclear. The Examiner further rejected claims 1 and 13 for indefiniteness with respect to the term "receptor expression", for being unclear as to whether "expression" relates to the expression of the gene encoding the receptor or to a change in the number of receptors. Applicant asserts that claims 1 and 13 have a clear and definite meaning when construed in the light of the specification. The specification as filed provides a clear definition of alpha (2) macroglobulin "receptor activity'. In particular, examples of alpha (2) macroglobulin receptor activities include binding activity, antigen presentation, endocytosis, activation of cytotoxic T cell activity, cell signaling activities, and chemotactic activities (see page 10, lines 26-34; page 25, lines 12-30; page 32, line 25; page 33, line 10; and page 38, line 36). Given the numerous examples of "receptor activity" disclosed in the text, one of skill in the art would be able to comprehend with clarity the meaning and scope of the term "receptor activity" of claims 1 and 13.

In addition, Applicant asserts that the term "receptor expression" in claims 1 and 13 refers to either receptor gene expression and/or receptor gene product expression. The specification discloses both alpha (2) macroglobulin receptor gene product expression and alpha (2) macroglobulin receptor gene expression (see page 10, lines 26-34 of the specification). Additionally, the claimed method also encompasses alpha (2) macroglobulin

receptor gene expression. Gene expression, and compounds which modulate such expression, are discussed in Section 5.6.2, beginning at page 53 of the specification. Furthermore, at page 28, lines 3-13, both types of expression are cited in the context of methods for identifying compounds that modulate an HSP-alpha (2) macroglobulin receptor-mediated process. In addition, new dependent claims 67 and 68 have been added to encompass embodiments of the invention wherein the expression refers to either alpha (2) macroglobulin receptor gene product expression or gene expression (see page 28). Thus, one of skill in the art would readily understand that the metes and bounds of the claims to include any measure of alpha (2) macroglobulin activity, gene expression or gene product expression.

Second, as to the rejection page 2, ¶ 4B of the Office Action, the Examiner asserts that Claim 17 is ambiguous, contending that the term "analog" is redundant to the term "derivative". In response, claim 17 has been amended to delete the term "analog" for redundancy. Applicant requests that the rejection be withdrawn in view of the claim amendment.

Third, on pages 2-3, ¶ 4C of the Office Action, claim 1 was rejected, the Examiner contending that it is unclear how receptor activity or receptor expression can be measured, claiming that it at best is drawn to determining the change in the binding of hsp and the α2M receptor. In reply, the Applicant asserts that the specification discloses numerous methods for measuring activity related to HSP-α2M receptor-mediated processes. As indicated in the specification, the activity indicative of an HSP-α2M receptor-mediated processes need not be a direct activity of the receptor, such as binding assays, but may also include indirect effects of downstream signaling events. Examples of assays that can be employed to measure such activity are found throughout the specification, see, *e.g.*., binding and/or labeling assays disclosed at page 8, line 16 and page 31, line 30; assays for stimulation of cytotoxic T cells disclosed at page 26, line 25 and page 69, line 32; assays for cellular uptake of HSP disclosed at page 32, line 5; downstream signaling assays and antigen presentation assays disclosed at page 32, line 18; assays for chemotactic activity measured are disclosed at page 33; and assays for calcium ion concentration measured are disclosed at page 33, line 20. Thus, given the ample description in the specification of assays which can be used to measure HSP-α2M receptor-mediated processes, by assaying receptor activity or receptor expression, one skilled in the art could readily understand what is meant by measuring receptor activity or receptor expression and therefore the bounds of the claim are distinct.

Finally, on page 3, ¶ 4D of the Office Action, Claim 14 was rejected as indefinite based on the term "interact." Claim 14 has been amended to recite "bind" rather than "interact." The rejection is therefore obviated.

In view of the forgoing arguments and amendments, Applicant respectfully requests the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph and request allowance of the pending claims.

CONCLUSION

Applicant respectfully requests that the present amendment and remarks be made of record in the instant application. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is believed that no fee is required for filing this Amendment. In the event a fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: May 28, 2002

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Enclosures

EXHIBIT A
MARKED-UP VERSION OF THE AMENDED CLAIMS
U.S. Patent Application Serial No. 09/625,137
(Attorney Docket 8449-123)

1. (amended) A method for identifying a compound that modulates a heat shock protein (HSP)-alpha (2) macroglobulin (α2M) receptor-mediated process, comprising:

(a) contacting a test compound with: [a heat shock protein and] (i) an isolated alpha (2) macroglobulin receptor, or a ligand-binding fragment thereof; and (ii) a purified heat shock protein, or a binding fragment thereof, or a purified HSP-peptide complex; and

(b) measuring the level of alpha (2) macroglobulin receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-α2M receptor-mediated process is identified.

2. (amended) The method of claim 1, in which the compound identified is an antagonist which interferes with [the interaction of the heat shock protein with the alpha (2) macroglobulin receptor, further comprising the step of:

(c) determining whether the level interferes with the interaction of the heat shock protein and the alpha (2) macroglobulin receptor.] an HSP-α2M receptor-mediated process.

11. (amended) The method of claim 1, in which the compound is an agonist which enhances [the interaction of the heat shock protein with the alpha (2) macroglobulin receptor] an HSP-α2M receptor-mediated process.

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13. (amended) A method for identifying a compound that modulates an HSP-α2M receptor-mediated process, comprising:

(a) contacting a test compound with: [a heat shock protein and] (i) an alpha (2) macroglobulin receptor- or ligand binding fragment- expressing cell; and (ii) a purified heat shock protein, or a binding fragment thereof, or a purified HSP-peptide complex; and

(b) measuring the level of alpha (2) macroglobulin receptor binding activity [or expression] in the cell,

such that if the level of binding activity [or expression] measured in (b) differs from the level of alpha (2) macroglobulin receptor binding activity in the absence of the test compound, then a compound that modulates an HSP-α2M receptor-mediated process is identified.

14. (amended) The method of claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to [interact with] bind to a heat shock protein.

17. (amended) The method of claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to [interact with] bind to a heat shock protein, wherein measuring the level of alpha (2) macroglobulin receptor activity of step (b) comprises[:

(a) contacting a heat shock protein with an alpha (2) macroglobulin receptor, or fragment, or analog, derivative or mimetic thereof, in the presence of a test compound; and

(b)]measuring the amount of heat shock protein, or binding fragment thereof, bound to the alpha (2) macroglobulin receptor, or ligand-binding fragment, [analog, derivative or mimetic] thereof,

such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the α2M receptor is identified.

18. (amended) The method of claim [17] 1 or 14 in which the alpha (2) macroglobulin receptor contacted in step (a) is on a cell surface.

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19. (amended) The method of claim [17] 1 or 14, wherein the alpha (2) macroglobulin receptor is immobilized to a solid surface.

21. (amended) The method of claim [17] 14 wherein the amount of bound heat shock protein is measured by contacting the cell with a heat shock protein-specific antibody.

22. (amended) The method of claim [17] 14 wherein the heat shock protein is labeled and the amount of bound heat shock protein is measured by detecting the label.

EXHIBIT B
PENDING CLAIMS
U.S. PATENT APPLICATION SERIAL NO. 09/625,137
(ATTORNEY DOCKET 8449-123)
(as amended under 37 C.F.R. §1.111)

1. A method for identifying a compound that modulates a heat shock protein (HSP)-alpha (2) macroglobulin (α2M) receptor-mediated process, comprising:

(a) contacting a test compound with: (i) an isolated alpha (2) macroglobulin receptor, or a ligand-binding fragment thereof; and (ii) a purified heat shock protein, or a binding fragment thereof, or a purified HSP-peptide complex; and

(b) measuring the level of alpha (2) macroglobulin receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-α2M receptor-mediated process is identified.

2. The method of claim 1, in which the compound identified is an antagonist which interferes with an HSP-α2M receptor-mediated process.

3. The method of claim 1, in which the test compound is an antibody specific for the alpha (2) macroglobulin receptor.

4. The method of claim 1, in which the test compound is an antibody is specific for alpha (2) macroglobulin.

5. The method of claim 1, in which the test compound is an antibody is specific for a heat shock protein.

6. The method of claim 1, in which the test compound is a small molecule.

7. The method of claim 1, in which the test compound is a peptide.

8. The method of claim 7, in which the peptide comprises at least 5 consecutive amino acids of the alpha (2) macroglobulin receptor (SEQ ID NO.: 7).

9. The method of claim 7, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin (SEQ ID NO.: 4).

10. The method of claim 7, in which the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

11. The method of claim 1, in which the compound is an agonist which enhances an HSP-α2M receptor-mediated process.

12. The method of claim 1 in which the HSP-α2M receptor-mediated process affects an autoimmune disorder, a disease or disorder involving disruption of antigen presentation or endocytosis, a disease or disorder involving cytokine clearance or inflammation, a proliferative disorder, a viral disorder or other infectious disease, hypercholesterolemia, Alzheimer's disease, diabetes, or osteoporosis.

13. A method for identifying a compound that modulates an HSP-α2M receptor-mediated process, comprising:

(a) contacting a test compound with an alpha (2) macroglobulin receptor- or ligand binding fragment- expressing cell and a purified heat shock protein, or fragment thereof, or a purified HSP-peptide complex; and

(b) measuring the level of alpha (2) macroglobulin receptor binding activity in the cell,

such that if the level of alpha (2) macroglobulin receptor binding activity measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-α2M receptor-mediated process is identified.

14. The method of claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to bind to a heat shock protein.

17. The method of claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to bind to a heat shock protein, wherein measuring the level of alpha (2) macroglobulin receptor activity of step (b) comprises measuring the amount of heat

shock protein, or binding fragment thereof, bound to the alpha (2) macroglobulin receptor, or ligand-binding fragment thereof,
such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the α2M receptor is identified.

18. The method of claim 1 or 14, in which the alpha (2) macroglobulin receptor contacted in step (a) is on a cell surface.

19. The method of claim 1 or 14, wherein the alpha (2) macroglobulin receptor is immobilized to a solid surface.

20. The method of claim 19 wherein the solid surface is a microtiter dish.

21. The method of claim 14 wherein the amount of bound heat shock protein is measured by contacting the cell with a heat shock protein-specific antibody.

22. The method of claim 14 wherein the heat shock protein is labeled and the amount of bound heat shock protein is measured by detecting the label.

23. The method of claim 22 wherein the heat shock protein is labeled with a fluorescent label.

64. The method of claim 1 or 13, wherein the alpha (2) macroglobulin receptor is purified.

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65. The method of claim 1 or 13, wherein the expression measured is alpha (2) macroglobulin receptor gene expression.

66. The method of claim 1 or 13, wherein the expression measured is alpha (2) macroglobulin receptor gene product expression.

67. The method of claim 14, wherein the derivative, analog, fragment, or domain of the alpha (2) macroglobulin receptor is purified.

68. A method for identifying a compound that modulates an HSP-α2M receptor-mediated process, comprising:

(a) contacting a test compound with an alpha (2) macroglobulin receptor-expressing cell and a purified heat shock protein, or fragment thereof, or a purified HSP-peptide complex; and

(b) measuring the level of alpha (2) macroglobulin receptor activity by a signal transduction activity assay, heat shock protein uptake assay, chemotaxis assay, or calcium ion concentration assays,

such that if the level of alpha (2) macroglobulin receptor activity measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-α2M receptor-mediated process is identified.

69. A method for screening a plurality of molecules for one or more molecules having the ability to modulate, directly or indirectly, the antigen presentation activity of alpha (2) macroglobulin receptor-expressing cells, comprising:

(a) contacting said plurality of molecules with the alpha (2) macroglobulin receptor-expressing cells and a purified complex of a heat shock protein and the antigenic peptide;

(b) measuring antigen presentation by said alpha (2) macroglobulin receptor-expressing cells in the presence of said plurality of molecules; and

(c) comparing antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells in the presence of said plurality of molecules with antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells in the absence of said plurality of molecules

wherein a lower or higher degree of antigen presentation indicates that one or more molecule(s) modulates the antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells.

70. A method for screening an antibody specific to a heat shock protein or an alpha (2) macroglobulin receptor for the ability to modulate, directly or indirectly, the antigen presentation activity of alpha (2) macroglobulin receptor-expressing cells, comprising:

(a) contacting the antibody with the alpha (2) macroglobulin receptor-expressing cells and a purified complex of a heat shock protein and the antigenic peptide;

(b) measuring antigen presentation by the alpha (2) macroglobulin receptor-expressing cells in the presence of the antibody; and

(c) comparing antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells in the presence of the antibody with antigen presentation activity by the alpha (2) macroglobulin receptor-expressing cells in the absence of the antibody,

wherein a lower or higher degree of antigen presentation indicates that the antibody modulates the antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells.

71. A method for screening a molecule for the ability to modulate, directly or indirectly, the antigen presentation activity of alpha (2) macroglobulin receptor-expressing cells, comprising:

(a) contacting the molecule with purified alpha (2) macroglobulin receptor-expressing cells and a purified complex of a heat shock protein and an antigenic peptide;

(b) measuring antigen presentation by the alpha (2) macroglobulin receptor-expressing cells in the presence of the molecule; and

(c) comparing antigen presentation activity by the alpha (2) macroglobulin receptor-expressing cells in the presence of the molecule with antigen presentation activity by the alpha (2) macroglobulin receptor-expressing cells in the absence of the molecule,

wherein a lower or higher degree of antigen presentation indicates that the molecule modulates the antigen presentation activity by said alpha (2) macroglobulin receptor-expressing cells.

72. A method for screening a plurality of molecules for one or more molecules having the ability to modulate, directly or indirectly, the ability of an alpha (2) macroglobulin receptor-expressing cell to stimulate the activation of cytotoxic T cells *in vitro* comprising:

(a) contacting said plurality of molecules with: (i) cells expressing alpha (2) macroglobulin receptor; (ii) a purified complex of a heat shock protein and a peptide; and (iii) cytotoxic T cells, under conditions conducive to the activation of cytotoxic T cells;

(b) comparing the activation *in vitro* of said T cells with the activation *in vitro* of T cells in the absence of said plurality of molecules,

wherein a lower or higher degree of T cell activation indicates that one or more molecules in said plurality of molecules modulates the ability of the alpha (2) macroglobulin -expressing cells to stimulate the activation of cytotoxic T cells against the peptide.

73. A method for screening an antibody specific to a heat shock protein or an alpha (2) macroglobulin receptor for the ability to modulate, directly or indirectly, the ability of an alpha (2) macroglobulin receptor-expressing cell to stimulate the activation of cytotoxic T cells *in vitro* comprising:

(a) contacting the antibody with: (i) cells expressing alpha (2) macroglobulin receptor; (ii) a purified complex of a heat shock protein and a peptide; and (iii) cytotoxic T cells, under conditions conducive to the activation of cytotoxic T cells;

(b) comparing the activation *in vitro* of said T cells with the activation *in vitro* of T cells in the absence of said plurality of molecules,

wherein a lower or higher degree of T cell activation indicates that the antibody modulates the ability of the alpha (2) macroglobulin -expressing cells to stimulate the activation of cytotoxic T cells against the peptide.

74. A method for screening a molecule for the ability to modulate, directly or indirectly, the ability of an alpha (2) macroglobulin receptor-expressing cell to stimulate the activation of cytotoxic T cells *in vitro* comprising:

(a) contacting said molecule with: (i) purified cells expressing alpha (2) macroglobulin receptor; (ii) a purified complex of a heat shock protein and a

peptide; and (iii) cytotoxic T cells, under conditions conducive to the activation of cytotoxic T cells;

(b) comparing the activation *in vitro* of said T cells with the activation *in vitro* of T cells in the absence of said plurality of molecules,

wherein a lower or higher degree of activation indicates that one or more molecules in said plurality of molecules modulates the ability of the alpha (2) macroglobulin -expressing cells to stimulate the activation of cytotoxic T cells against the peptide.

75. The method of any one of claims 70, 71, or 72, wherein the activity is measured by a cytokine release assay.

76. The method of any one of claims 13, 69, 70, 71, 72, 73, or 74, wherein the alpha (2) macroglobulin receptor is recombinantly expressed in the cell.